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Part IV

Department of Health, Education, and Welfare

Public Health Service

National Toxicology Program; Meeting

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Public Health Service

National Toxicology Program; Meeting

The Director of the recently established National Toxicology Program (NTP) announces an open meeting on August 10, 1979, for the purposes of presenting an overview of the FY 1979 Annual Plan, receiving comments and questions on the Annual Plan and the future directions of the NTP, and receiving recommendations for compounds to be tested in the future. Part I of the FY 1979 Annual Plan, describing the NTP's current year efforts and resources, is printed in its entirety immediately following this announcement. Part II of the Plan is a "Review of Current DHEW Research Related to Toxicology" and is available upon request.

Copies of the complete Annual Plan, Parts I and II, as well as copies of the Program's establishment document referred to in the **Federal Register**, November 15, 1978, pp. 53060–53061, can be obtained by calling: Ms. Leslie Gardner at (919) 541–3267 or FTS 629–3267.

The meeting will begin at 10:00 a.m. and will be held in the main auditorium of the HEW North Building, 330 Independence Avenue, S.W., Washington, D.C. Dr. David P. Rall, Director of the National Toxicology Program, and key staff from the participating HEW agencies in the NTP will describe the FY 1979 Annual Plan and the agency resources dedicated to the NTP. Dr. Eula Bingham, Assistant Secretary of Labor for Occupational Safety and Health, and Chairman of the NTP's Executive Committee will briefly describe the role of the light-member Executive Committee. Executive Committee members will attend as schedules permit.

Key NTP agency staff will be available to receive comments and questions from the public from 11:00 a.m. to 12:00 noon and from 1:00 p.m. to 5:00 p.m. unless the comments from those in attendance have been received prior to that time.

It is requested that persons planning to attend the August 10, 1979, meeting give advance notice to: Ms. Leslie Gardner (telephone: (919) 541–3267 or FTS 629–3267), National Toxicology Program, P.O. Box 12233, Research Triangle Park, N.C. 27709.

All written comments on the Annual Plan are welcome and will be received and considered through August 17, 1979. All written comments as well as requests for additional information regarding this meeting should be addressed to: Dr. David P. Rall (telephone: (919) 541–3201 or FTS 629–3201), Director, National Toxicology Program, P.O. Box 12233, Research Triangle Park, N.C. 27709.

Dated: July 18, 1979.

David P. Rall,

Director, National Toxicology Program.

Department of Health, Education, and Welfare; National Toxicology Program

Annual Plan for Fiscal Year 1979

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Department of Health, Education, and Welfare; National Toxicology Program

Annual Plan for Fiscal Year 1979

Background

On November 15, 1978, Secretary Califano announced the establishment of the National Toxicology Program. The broad goal of this Program is to strengthen the Department's activities in the testing of chemicals of public health concern as well as in the development and validation of new and better integrated test methods. Specific goals for the Program are:

(1) To broaden toxicological characterization of those chemicals being tested.

(2) To increase the rate of chemical testing, within the limits of available resources.

(3) To develop and begin to validate a series of protocols more appropriate for regulatory needs.

To accomplish these goals the Program was established as a Departmentwide effort to provide needed information to regulatory and research agencies and to strengthen the science base. The Program is at present comprised of the relevant activities of the Food and Drug Administration (FDA), the National Cancer Institute (NCI), the Center for Disease Control/National Institute for Occupational Safety and Health (CDC/NIOSH), and the National Institute of Environmental Health Sciences (NIEHS). It will be planned, programmed, and carried out as a coordinated whole under the direction of Dr. David P. Rall who will continue to serve as Director, National Institute of Environmental Health Sciences and for the purpose of this Program reports to the Assistant Secretary for Health. The resources available to the Program in FY 79 are dedicated by components of the FDA, NCI, NIEHS, and NIOSH and total to $41,000,000.

Central to the effective planning, coordination and operation of the National Toxicology Program is the development and approval of an annual plan.

This plan is to include:

A review of current DHEW research as it relates to toxicology.

Specification of the Program activities and resources to be managed by the Program Director:

Current toxicology testing capacity (i.e. Dollars, positions, and space) and how that capacity is being utilized.

Amount of test capacity which may be available in the coming year.

Plans for test development and validation of test systems which take into account research opportunities and needs of the field.

The compounds to be tested, the test procedures to be followed, and a schedule for the tests.

The regulatory and scientific opportunities which were considered in the development of the plan.

Recommendations of the Program Director as to the resources needed for the Department's toxicology program capacity. (This section will first be

included in the second plan, to be completed by September 1, 1979.)

Introduction

The National Toxicology Program will, in its first year of operation, identify the unifying themes that exist in the current toxicology programs of the four NTP research agencies. The first year's operation, will bring about several adjustments that move toward fulfillment of the broad Program objectives. In the four months since establishment of the Program, it has become clear that several of the toxicological programs which were at various stages of development in the individual agencies were designed to achieve closely similar goals. Integrating these important activities will provide added impetus to the Program's goals during the first year of operation. In addition, several new initiatives were developed and will be implemented because of opportunities provided by the existence of the NTP. These new and revitalized initiatives, along with the ongoing toxicological activities of the four NTP agencies, are described in the first Annual Plan. Because of the limited time available to prepare the first Annual Plan, it was possible to incorporate only brief descriptions of planned activities. A more detailed presentation of NTP activities will be contained in the second Annual Plan, to be developed for September 1, 1979.

One of the major objectives of the NTP is to create stronger links between research devoted to the development and validation of new or improved toxicological methods and the needs of the regulatory community for such methods. There is the additional objective of ensuring efficient and proper toxicological evaluation of substances that may pose a threat to the public health and which, therefore, may require regulation. Meetings of the Executive Committee and Committee staff have led to the identification and prioritization of compounds to be subjected to toxicological evaluation and to the specification of several areas of research in methods development and validation that are considered of central importance to both the research and the regulatory agencies. Thus, the major objectives of the NTP will begin to be realized immediately.

In addition, during the first year several management functions common to many Program activities, and heretofore carried out somewhat independently by the member agencies, will be centralized, thereby increasing the efficiency of operating HEW's toxicology programs. Among the common functions to be centralized are: chemical intelligence; data management and analysis; laboratory animal production and quality control; chemical repository; and technical information and reports.

A major initiative will be the creation of a management function that insures that the quality of the Program's initiatives are consistent with good laboratory practices.

The toxicology activities of the NTP agencies are moving in directions generally consistent with Program objectives. The goal of the first year is to isolate activities that can be made to move quickly toward Program objectives. During this process dialogue between research and regulatory scientists will increase and this is critical to the Program's success because it is not always readily apparent if and how specific forms of research will serve a regulatory need. Only through such a dialogue will new ideas for research develop. And it is only through the development of such ideas that new program initiatives, and the resource shifts they will require, can be put into place.

The Director has established an internal Steering Committee to advise him on direct Program operation and prioritization. It is composed of the Deputy Director, NTP (Dr. J. Moore), and the science program leaders of the contributing agencies: Acting Director, NCTR (Dr. T. Cairns); Acting Scientific Director, NIEHS (Dr. D. Hoel); Associate Director, Carcinogenesis Testing Program, NCI (Dr. R. Griesemer); and Director, Division of Biomedical and Behavioral Science, NIOSH (Dr. E. Harris).

Chemical Selection and Intelligence

The development of lists of chemicals to be tested is a most important task if the resources available to the NTP are to be effectively utilized. Each agency represented on the Executive Committee was asked to propose testing initiatives and to participate in the ordering of chemicals. The principles for selection of these compounds included such factors as estimated or known extent and intensity of human exposure, estimated or known severity of toxicological effects, and the scientific needs to compare testing methodologies and to study structure activity relationships. The NTP is concerned about its appropriate role in Government sponsored testing as it relates to the responsibility of the private sector to bear the burden of chemical testing as mandated by specific Federal laws or statutes. The NTP is in the process of developing a set of principles for selecting chemicals that will incorporate the previously listed factors and concerns.

The selection of a chemical does not *a priori* commit it to testing by NTP. It does commit the NTP to ascertain the specific toxicologic and regulatory concerns, evaluate the adequacy of existing data or current efforts in Government, academic, or private laboratories, and then propose and conduct specific test(s) that are needed.

A single focus for this activity has been established to insure the future provision of a standard base of information on each chemical nominated. This standard base of information will include chemical name, Chemical Abstract Series (CAS) No., commercial formulations, use(s), human exposure, known or suspected health effects, existence, and adequacy, of relevant toxicologic data and specific areas of needed toxicologic research. Once a chemical has been selected for testing, this group will provide the pertinent science information for proper design of the test protocol. Existing data resources will be utilized for these activities.

Data Management and Analysis

The National Toxicology Program needs are: 1) data acquisition, storage, and retrieval, 2) data reduction and analysis, and 3) management tracking and control.

Data Acquisition, Storage and Retrieval. The most complex and highest priority need is data management of lifetime bioassays. Current systems lack an automated data input system and quality control features at the testing laboratory. The NTP has selected the developing TDMS (Toxicology Data Management System), a modular system, for continued prototype development and on-line installation at three laboratory facilities in early 1980 with additional installations also projected later in the year.

Data management in the area of mutagenesis is the next highest priority because of the potentially large quantities of data to be generated. Existing and developing systems will be used.

Management Information. High priority is given to early development of a simple system that should provide on-line information on chemicals selected for testing, the nature of the test(s) and test status.

Data Analysis. Appropriate statistical methodologies for data analysis of microbial mutagenesis and teratology

assays are to be developed in FY 79. The statistical methodologies used for carcinogenicity data will be reviewed and will require considerable methodologic research. Methodologies for statistical analyses of other toxicology data will be reviewed and revised, as necessary, as routine testing capability is initiated.

Laboratory Animal Production and Quality Control

The $B_6C_3F_1$ mouse and Fischer 344 rat will continue to the principal test species. Animal production resources will continue to be developed and maintained to provide animals to chemical testing laboratories. Basic standards for husbandry and care as they specifically relate to toxicology testing are also being developed. A standard controlled, open formula test diet is to be selected and incorporated into the test protocols.

Although the current NTP strains provide meaningful toxicology and carinogencity data, the test animal is such a vital selection in experimental design that an evaluation of the continued utility of these or other rat and mice strains is planned. The $B_6C_3F_1$ mouse and Fischer 344 rat are genetically uniform (isogenic) strains which is a desirable trait for toxicity testing. It has been proposed that the use of several isogenic strains in a bioassay would provide a better extrapolation base than the use of a single strain. The statistical power of data developed in several isogenic strains appears to be equivalent to, and may exceed, current practices of using single strains. A course of study to develop and validate a series of experimental designs using multiple isogenic strains is planned.

Chemical Repository

A central repository for chemicals tested by the NTP will be established from which the procurement, analyses, distribution, reference archiving, and quality assurance of chemicals during test use will be directed. The operation of a variety of existing capabilities will be integrated for the performance of this activity.

Technical Information and Reports

The Annual Plan describes research dealing with the testing of more than 500 chemicals, with many being utilized in a variety of tests. The chemical selection process should lead to the Program testing chemicals or validating methods that are of significant scientific and regulatory interest; therefore, these results need to be promptly communicated. In developing a mechanism for the orderly processing and announcement of NTP research, the use of established "online" computer systems as an adjunct to published documents is being considered as is the feasibility of using the capabilities of the Toxicology Information Program, and the National Library of Medicine.

A high priority is to establish a process for scientific review of the adequacy of the test data developed by the NTP.

The NTP will continue to develop the Environmental Mutagen Information Center (EMIC) and the Environmental Teratology Information Center (ETIC). The development of online extracts of the ETIC entries is scheduled to commence in late 79. Priority of extract preparation will be given to those chemicals of interest to the NTP.

Teratology

Chemical teratology testing traditionally has focused on detecting anatomical malformations that occur during *in utero* development through the systematic examination of the fetus (by the naked eye or low magnification) for organ, limb, or skeletal abnormalities. Analysis and interpretation attempts to discriminate between effects caused by maternal toxicity, fetal toxicity, or death. In recent years experiments have clearly identified that functional abnormalities without gross malformations can result from chemical exposure during development; behavioral abnormalities are a principal example. Several foreign countries have recently imposed general requirements for behavioral teratology; the Toxic Substances Control Act may also mandate such testing. Therefore, it is imperative that the relevance and validity of behavioral teratology test procedures be established. The NTP will coordinate and conduct a collaborative validation of test procedures.

It is proposed that 4–6 test methods, which appear to have the greatest potential utility, will be utilized in six laboratories using standard chemicals. Recommendations concerning the incorporation of behavioral teratology methods into reproduction and teratology testing guidelines should be possible, based on the results of these studies. This project will encompass 2–3 years.

Current methods do provide meaningful data about the teratogenic potential of chemicals. To insure that all scientific data gathered during these evaluations are most effectively utilized, a selected analysis of chemicals, for which there is definitive human and animal teratology information, is being performed.

In addition, existing laboratory data bases will be examined to determine the range of dose parameters that indicate linearity of response and permit the development or identification of appropriate biomathematical procedures for low dose risk estimation.

A systematic histopathologic examination of fetuses will be conducted and compared with the results obtained using traditional methods as part of the teratology testing of 8–10 coded chemicals. Chemicals selected for teratologic evaluation are listed in Table 1; additional nominations are listed in Table 2.

Mutagenesis

Mutagenicity assays should identify structural or functional DNA disturbances in germ or somatic cells. The former is of interest for predicting potential undesirable effects on fertility, the developing conceptus, or in generations subsequent to that which received chemical exposure. Somatic mutation may predict physiologic alterations in the exposed person and the potential for cancer.

A major goal is to establish a battery or matrix of procedures which, when used as a prescreen, can aid in establishing priorities for indepth animal studies.

A systematic evaluation of the utility and predictive value of various *in vitro* test systems will continue. Specifically, these efforts are directed toward:

1) Development, definition and standardization of methods for routine testing.

2) Determination of the intralaboratory and interlaboratory reproducibility of defined protocols.

3) Evaluation of tests using coded chemicals and representing different chemical classes of known mutagenic activity.

A *Salmonella*/microsome plate assay has been standardized and found to yield reproducible results within and between several laboratories. This protocol uses *Salmonella typhimurium* strains TA 1535, 1537, 1538, 98 and 100 with and without metabolic activation. The liver S–9 preparations are prepared from both uninduced and Arochlor 1254 induced Fischer 344 rats, $B_6C_3F_1$ mice or Syrian hamsters. A series of 45 chemicals (Table 3) which have been tested by lifetime bioassays in Fischer 344 rats and $B_6C_3F_1$ mice, and for which stable lots of the original chemical are available, are to be assayed. The purpose of the testing is to determine whether the same type of species

variation observed in the animal bioassays will be detected in the mutagenicity assays. Each chemical will be tested under code in four laboratories which will further establish the interlaboratory reproducibility.

Other assays being developed or validated include *Escherichia coli* WP2 uva, pol A+ and pol A and the mammalian systems L5178Y mouse lymphoma [TK+/locus] and ARL6 rat liver.

Using the validated standardized assays, an *in vitro* testing capability has been established using *Salmonella typhimurium* strains TA 1535, 98, 1537, and 100 (with and without metabolic activation). A total of 180 chemicals will be tested in the remainder of FY 79. The planned capacity for testing in FY 80 is 300. The chemicals selected for assay are listed in Table 4. Chemicals selected for extensive toxicologic characterization, including carcinogenicity (Table 9), will be priority additions to this list.

An *in vitro* mammalian cytogenetics capability (chromosome aberration including sister chromatid exchange) will be established in FY 79. System validation will be required and it is planned to test 45 chemicals in FY 80 assuming successful validation. The goal is to expand this capability so that it can become an integral part of the initial screen along with the *Salmonella* assays.

The determination of mutagenicity can range from a set of tests which merely alert as to mutagenic potential to more extensive tests which firmly establish the presence (or lack) of mutagenicity and specify the specific type of genetic lesion produced. When large numbers of chemicals are to be tested, it is not feasible to employ an entire battery of tests simultaneously; thus, it is planned to apply a sequential array of tests. The current initial screens are the *S. typhimurium* assays previously described and the *in vitro* cytogenetic assay if validated. Chemicals that are mutagenic in these assays will be subject to further testing. (Selected chemicals that are negative in the initial screen may receive further testing, taking into account such factors as known biologic activity of related compounds and level of human exposure.) The second sequence of testing will utilize *Drosophila spp.* which possesses some inherent chemical metabolism capability and can provide more precise information on the types of mutations induced, the time course of induction, and, in addition, demonstrate heritability of the induced mutation. Regular test capability in *Drosophila* will be established in FY 79 with an aim being the assay of 20 chemicals per year commencing in FY 80.

Eighteen chemicals (Table 5) are to be tested in rats for *in vivo* mutagenic activity using a dominant lethal assay, bone marrow karyotyping or sperm abnormality evaluation. Selective use of *Drosophila* recessive lethal and unscheduled DNA repair in human cell lines is also planned. Some of these tests also have utility for assessing reproductive function.

The NTP has assumed support and participation in an international collaborative study, under the auspices of the International Association of Environmental Mutagen Societies, with the objective of systematically evaluating a range of mutagenicity assay systems for their ability to predict chemical carcinogenicity. The responses of approximately 25 assay systems will be determined for 42 coded reference carcinogens and noncarcinogens. The chemicals to be tested and the assay systems to be employed are listed in Table 6 and 7, respectively. All assays are to be completed in FY 79 with decoding and combined analysis scheduled for the first quarter of FY 80.

The assessment of mutagenic risk to future generations with our current state of knowledge must utilize whole mammal experiments on heritable damage. There are examples of noncorrelation between microbial tests and of heritable effect determinations in the mouse. An NTP goal is to develop a logic for the proper use and utility of *in vivo* mammalian genetic tests. The heritable translocation assay will be further evaluated in this regard. Other methods that need evaluation or development involve the role of repair in mammalian mutation induction and the role of the female in determining heritable mutagenic risk.

Carcinogenesis

A lifetime bioassay in rodents is the current procedure utilized to determine carcinogenic potential of a chemical. The NTP does not propose alternative methods but acknowledges a need in the longer term, to develop or validate less expensive and more rapid methods that may in some instances supplant the need for lifetime bioassays.

Mammalian cell transformations are potential short-term assays that indicate carcinogenic potential of a chemical. Transformation assays being evaluated include BALB/c 3T3, Fischer Rat Embryo (RLV infected), Hamster embryo, and C3H 10T½. In this effort the first 15 chemicals listed in Table 3 will be tested for transforming potential in the hamster embryo clonal assays and in the BALB/c 3T3 focus assay.

The results of *Salmonella* assays will be considered in prioritizing the order in which a chemical may be tested in lifetime bioassays. Other assays, once validated, that will augment the microbial assays, include cell transformation, or other *in vitro* and *in vivo* assays described in the mutagenesis segment of the Annual Plan.

A substantial body of literature exists related to short term *in vivo* carcinogenicity testing, but no model is sufficiently validatd to be applied to the routine testing of chemicals. One model, the mouse lung adenoma system, is sufficiently developed to be selected for indepth validation. During FY 79 a validation protocol will be developed for contract award and initiation. Seventy-five to 100 chemicals will be selected, giving preference to those chemicals for which adequate lifetime bioassay data exist, or are in progress, with selections balanced to insure a broad representation of chemical classes. The results of this study, along with *in vitro* microbial mutagenesis data and findings of lifetime rodent bioassays, will be compared in evaluation of the mouse lung adenoma system.

Rat liver assay systems will also be reviewed in order to determine what specific areas of methods development need to be pursued.

A literature search and analysis will permit comparison of the results of animal bioassays and mutagenesis tests with results of mouse lung, skin painting and subcutaneous assays. Particular attention will be given to: a) the concordance of *in vitro* fibroblast transformation and subcutaneous sarcoma formation, and b) to skin tumor production in Syncar versus non-Syncar mice. The results of this analysis will be considered in developing NTP initiatives for FY 80.

There are diferent viewpoints as to what constitutes the best design of lifetime bioassays. Areas of differing opinion include choice of species and strain, age at exposure, route of exposure, number of doses tested, dose levels, and of methods used in analysis. An NTP priority is to review and possibly revise the current lifetime bioassay design consistent with the projected use of the bioassay results.

Carcinogenicity testing traditionally begins with young adult animals (typically six-week old rodents). Human chemical exposures may include the period of *in utero* development and infancy as well as continued lifetime

exposure. These exposures occur through exposure of pregnant workers, use of drugs, and long-term accumulation and persistence of certain chemicals in the mother's body with secretion in milk. The adequacy of lifetime bioassay methods versus methods that also include prenatal and neonatal exposures is being evaluated. Four chemicals will be tested; polychlorinated biphenyl (Arochlor 1254) and phenytoin have been selected with 2 additional chemcials to be selected and testing started in FY 79.

The carcinogenic potential of chemical combinations has been described, the conversion of heterocyclic secondary amines to nitrosamines in the presence of NO_2 (N_2O_4) being a recent example. The ubiquity of NO_2 and the widespread distribution of heterocyclic amines prompt the hyothesis that some neoplastic diseases may be a consequence of *in vivo* interaction with these chemicals. A test of the hypothesis is planned in an animal bioassay using NO_2 exposure by inhalation and heterocyclic amine (2,6 dimethylmorpholine) exposure by the oral route.

Lifetime inhalation bioassays for carcinogenicity usually involve a duration of exposure that is arbitrarily determined. The specialized facilities required for inhalation studies are expensive and commit limited technical manpower and resources for extended periods of time. A study with rats, mice and hamsters is in progress that uses a design that varies the age of animals exposed and the duration of exposure to vinyl chloride, a known carcinogen. The objective of the study is to provide data that permit a species comparsion of tumor response and an analysis of the exposure regimens that provide a predicted carcinogenic response. The data may indicate that a period of exposure of less duration than is currently employed will provide a meaningful bioassay resut. These studies are projected for completion in FY 80.

The National Toxicology Program assumed responsibility for 147 chemicals being tested for carcinogenic potential in lifetime rodent bioassays (Table 8). Draft reports on 13 of these chemicals are expected to be completed in FY 79 and formally issued in early FY 80. An additional 106 chemicals have been selected for extensive toxicologic and carcinogenic evaluation (Table 9). Resources will permit testing to commence on 60 of these chemicals in FY 79 with testing of the remaining chemicals scheduled for FY 80. There are 104 chemicals (Table 10) that have been nominated for testing which will be evaluated for selection according to the procedures described on page 3 of the Annual Plan. Chemical nomination and selection is a continual process.

Toxicology

Chemicals selected for extensive toxicologic characterization (Table 9) will usually be evaluated in a series of acute and subacute experiments followed by chronic (lifetime) experiments when *in vivo* carcinogenicity data is desired. In the former experiments a core of traditional toxicology data will be recorded with additional screening efforts incorporated in such areas as neurobehavior, fertility and reproduction, immunotoxicology, renal toxicity and respiratory function as indicated by specific health concerns, toxicities associated with related chemicals, etc. When extensive toxicologic efforts are conducted, dose related data on absorption, disposition and metabolism will be collected.

A second initiative is to develop, validate and implement procedures for characterization of specific toxic parameters such as neurobehavior, pulmonary function, immunobiology and fertility and reproduction. Descriptive narrations of the major NTP toxicology initiatives are decribed below.

Behavioral Toxicology. Laboratories within the National Toxicology Program are actively engaged in the development of new methods and in the routine use of existing methods for testing the behavioral and neurological effects of a variety of toxic agents. However, the capacity for evaluating compounds is limited. The number of compounds can be substantially increased only through the contract mechanism. A battery of screening tests which will reflect the entire range of potential behavioral and neurologic tests and are sensitive and predictive for humans is needed. A basic test battery is currently being validated; in the interim, this test battery is being selectively used for chemical screening.

Specific experiments that characterize the nature of the effect and provide dose response data are planned for 16 select chemicals for which there is evidence of behavioral or neurological effects. These chemical are listed in Table 11.

Immunology. A number of chemicals have been found to cause immuno-suppression, with cell mediated immunity and the developing immune systems at particular risk. Several conferences have recently addressed this topic, and, whereas there is general agreement on the immune parameters to be assessed, there is considerable difference of opinion regarding the most appropriate techniques to be employed. The NTP will begin the development and validation of an immunology test battery as well as continue studies that estabish the role of immune assessment in toxicologic characterization.

Clinical Chemistry. A variety of tests have been utilized as indicators of organ function. The tests, in many instances, lack the sensitivity to detect deleterious effects at levels below those which are detectable through gross and histopathologic examination. A program will begin to identify more sensitive methods for detection of injury and subsequently aim at the development of inexpensive, accurate and automated methods that can be incorporated into routine testing procedures. Tests that assess hepatic and renal function will be emphasized initially.

Chemical Distribition and Metabolism. Specific isomers of the complex polychlorinated biphenyl mixture have been the subject of pharmacokinetic studies in several species (rat, dog, and Rhesus money). Results of current studies indicate a marked difference in the ability of the monkey to metabolize or excrete some of the more toxic isomers as compared to the rodent. These studies will be extended and will attempt to provide data that may suggest the appropriate laboratory species from which to extrapolate dose response data in assessing human risk.

Toxicology studies with chlorinated dibenzofurans indicate species variability as to the dose that causes toxic effects. Basic distribution and metabolism studies with $_{14}C$ labeled 2,3,7,8 TCDF will seek to establish if species difference is due to variation in chemical distribution, metabolism or excretion. These data should provide a logical means for selecting appropriate species for possible teratology and carcinogenicity studies.

Recent studies indicate that some benzidine derived dyes are metabolized with the formation of benzidine as a metabolite. Benzidine is a carcinogen. Additional benzidine derived dyes will be studied to determine if the formation of benzidine as a metabolite is typical of several classes of benzidine derived dyes.

Pulmonary and Cardiovascular Toxicity. The NTP has significant capacity for inhalation research and testing. A majority of the work that assesses cardiovascular and pulmonary toxicity is performed in NTP laboratories, whereas the inhalation exposures to assess carcinogenic

potential are performed by contract. The NTP recognizes the need to expand toxicologic assessment of inhaled chemicals to other than NTP laboratories. Methods development and validation is planned.

Chronic inhalation studies on the cardiovascular effects of methyl bromide will continue. Acute or chronic studies on pulmonary response are planned for four epoxides: butylene oxide, ethylene oxide, propylene oxide, and styrene oxide.

Lung fibrogenesis as a consequence of fibers and dusts is a major health concern. A variety of methods are being utilized in an attempt to assess fibrogenic effects including histophathology, fibroblastic activity *in vitro,* macrophage interaction, and bilogical availability using the isolated perfused lung. Chemicals that are being utilized in these studies include:

aluminum salts and organoaluminum
asbestos
copper compounds
fibrous glass
lead oxide
lead sulfide
silica
2 ethoxy ethanol
2 nitropropane

Studies on the dose related pathogenesis and persistence of noncarcinogenic effects of chlordecone in rats are in progress. Toxic parameters being studied include reproduction, fertility, neurobehavior, immunology, hepatotoxicity and blood clotting.

Table 1.—*Chemicals Selected for Teratology Studies*

Chemical	CAS No.
Caffeine	58-08-2
Dimethylaniline	87-62-7
Ethyl Benzene	100414
Ethylene oxide	75218
Ethoxy ethanol*	110-80-5
Formaldehyde	50-00-0
Lead monoxide**	
Pentachloroanisole	1825-21-4
Toluene	108883
Xylenes:	
O-Xylene	94576
M-Xylene	108383
P-xylene	106423

*Post natal behavioral and nervous system abnormalities will also be evaluated.

**Post natal renal, cardiovascular, metabolic and hematopoietic systems will be evaluated through 10 months of age.

Table 2.—*Chemicals Nominated for Teratology Studies or Screening for Teratogenic Effect*

Chemical	CAS No.
Bisphenol A	80-05-7
Butyl nitrite	
Capsaicin	404-86-4
Cinnamaldehyde	104-55-2
Chlorinated dibenzofurans	
Copper compound(s)	
P-dichlorobenzene	106-46-7

Table 2.—*Chemicals Nominated for Teratology Studies or Screening for Teratogenic Effect*—Continued

Chemical	CAS No.
Gentian violet (hexamethyl-p-rosaniline)	548-62-9
Mercaptobenzothiazole	149-30-4
Oil of nutmeg	
Sulfamethazine	57-68-1
Tocopherol	1406-66-2

Table 3.—*Chemicals Tested in Salmonella/Microsome Plate Assays for Comparison With Fischer 344 Rat and $B_6C_3F_1$ Mouse Lifetime Bioassays*

4-Amino-2-nitrophenol—119-34-6
2-Amino-5-nitrothiazole—121-66-4
p-Chloroaniline
3-Chloromethyl pyridine hydrochloride—6959-48-4
N,N'-Dicyclohexylthiourea—1212-29-9
4,4'-bis (Diemthylamino) benzophenone
Dyrene(anilazine)—101-05-3
Ethylene dibromide—106-93-4
Lithocholic acid—434-13-9
4,4'-Methylenebis(n,N'-dimethylaniline)—101-61-1
Nitrilotriacetic acid trisodium salt monohydrate
4-Nitro-o-phenylenediamine—99-56-9
2-Nitro-p-phenylenediamine—5307-14-2
3-Nitropropionic acid—504-88-1
p-Phenylenediamine—106-50-3
Acetylsalicylic acid—50-78-2
Aldicarb—116-06-3
Aniline hydrochloride—142-04-1
o-Anisidine hydrochloride—134-29-0
APD—8003-03-0
1,2,3-Benzotriazole—95-14-7
Caffeine—58-08-2
Cinnamyl anthranilate—87-29-6
tris(2,3-Dibromopropyl)phosphate—126-72-7
1,3-Dichloro-5,5-dimethylhydantoin—118-52-5
Fluometuron—2164-17-2
1,5-Naphthalenediamine—2243-62-1
Proflavin hydrochloride—952-23-8
Reserpine—50-55-5
Styrene—96-09-3
4'-Chloroacetyl(acetanilide)—140-49-8
Coumaphos—56-72-4
m-Cresidine—102-50-1
p-Cresidine—120-71-8
Diazinon—333-41-5
2,4-Dimethoxyaniline—54150-69-5
3,3'-Dimethoxybenzidine-4,4'-diisocyanate
ethylenediaminetetra acetic acid, sodium salt—60-00-4
3-Methyl-1-phenyl-2-pyrazotin-5-one
Nitrofen—1836-75-5
5-Nitro-o-toluidine—99-55-8
p-Quinone dioxime—105-11-3
Succinic acid 2,2-dimethylhydrazide—1596-84-5
2,5-Toluenediamine sulfate—6369-59-1
Triphenyltin—76-87-6

Table 4.—*Alphabetical List of Chemicals Selected for Salmonella Mutagenicity Assay*

Acetamide—60-35-5
Acetin—26446-35-5
N-Acetyl-o-toluidine—120-6-1
Acrolein—107-02-8
3-Amino-α·α·α-trifluorotoluene—98-16-8
o-Aminophenol—95-55-6
Amyl nitrite—463-04-7
Aniline—62-53-3
o-Anisidine—90-04-0
p-Anisidine—104-94-9
Anthracene—120-12-7
Arochlor 1254—11097-69-1
l-Aziridineethanol—
Azobenzene—103-33-3
Azodicarbonamide—123-77-3
Benzaldehyde—100-52-7
Benzofuran—271-89-6
p-Benzoquinone dioxime—105-11-3
Benzyl salicylate—118-58-1
Beta-methylumbelliferone—90-33-5
Beta-picoline—108-99-6
Biphenyl—92-52-4
2-Biphenylamine—90-41-5
4-Biphenylamine—92-67-1
2,4'-Biphenylamine—
2,4'-Biphenyldiamine—492-17-1
Bis(chlorendo)furan
Bisphenol—80-05-7
Boric acid—10043-35-3
Bromobenzene—108-86-1
Bromocyclohexanol
Bromoform—75-25-2
2-Butanone peroxide—1338-23-4
n-Butyl para-aminobenzoate—94-25-7
Cacodylic acid—75-60-5
Carbon disulfide—75-15-0
Catechol—120-80-9
Chloral hydrate—302-17-0
Chlorendic acid—115-28-6
2-Chloro-1,3-butadiene—126-99-8
4-Chloro-α·α·α-trifluorotoluene—98-56-6
4-Chloro-3,5-dinitro-α·α·α-trifluorotoluene—393-75-9
4-Chloro-3-nitro-α·α·α-trifluorotoluene
Chlorobenzene—108-90-7
4-Chloronitrobenzene—100-00-5
2-Chloronitrobenzene—88-73-3
m-Chlorophenol—108-43-0
o-Chlorophenol—95-57-8
p-Chlorophenol—106-48-9
Cinnamaldehyde—104-55-2
Copper acetoarsenite—12002-03-8
m-Cresol—108-39-4
o-Cresol—95-48-7
p-Cresol—106-44-5
Crotonaldehyde—123-73-9
Cyanuric acid—108-80-5
Cyclohexanol—108-93-0
Cyclohexanone—108-94-1
Diacetone acrylamide—2873-97-4
4,4'-Diamino-2,2'-stilbenedisulfonic acid
2,4-Diaminophenol hydrochloride—137-09-7
Debenzofuran—132-64-9
Diborane—19287-45-7
2,3-Dibromo-1-propanol—96-13-9
Di-n-butylamine—111-92-2
1,3-Dichlorobenzene—541-73-1
1,2-Dichlorobenzene—95-50-1
1,4-Dichlorobenzene—106-46-7
cis-Dichlorodiamine platinum—15663-27-1
Dichlorodiphenylethylene—72-55-9
trans-1,2-Diochlorethylene—540-59-0
cis & trans-1,2,3-Dichloroethylene—156-59-2
1,1-Dichloroethylene—75-35-4
3,4-Dichloronitrobenzene—99-54-7
2,3-Dichloronitrobenzene—3209-22-1
2,3-Dichlorophenol—576-24-9
2,5-Dichlorophenol—38048-58-7
2,6-Dichlorophenol—87-65-0

3,4-Dichlorophenol—95-77-2
3,5-Dichlorophenol—591-35-5
Diethanolamine—111-42-2
7-Diethylamino-4-methylcoumarin—91-44-1
Diethyl carbonate—105-58-8
Diethyldichlorosilane—1719-53-5
Diethyleneglycoldimethylether (diglyme)—111-96-6
Diethyl ethylphosphonate—78-38-6
Di(2-ethylhexyl) phthalate—117-81-7
5,7-Dihydroxy-4-methylcoumarin—2107-76-8
Diisobutylketone—108-83-8
Dimethoxane—828-00-2
1,2-Demthoxybenzene—91-16-7
Dimethylamine—124-40-3
Dimethyl cyanamide—1467-79-4
N,N-Dimethylformamide—68-12-2
2,4-Dimethylphenol—105-67-9
N,N-Dimethylurea—1320-50-9
trans-1,2-Dichloroethylene—156-60-5
cis & trans 1,2-Dichloroethylene—540-59-0
4,6-Dinitro-2-aminophenol—96-91-3
2,4-Dinitrotoluene—121-14-2
Dioctyladipate—123-79-5
1,4-Dioxane—123-91-1
Diphenyl oxide (diphenyl ether)—101-84-8
1,2-Epoxypropane—75-56-9
Ethyl bromide—74-96-4
Ethyl chloride—75-00-3
Ethylene glycol—107-21-1
Ethylenediamine—107-15-3
2-ethylhexyl diphenyl phosphate—1241-94-7
Eugenol—97-53-0
Ferrocene—102-54-5
1-Fluoro-2,4-dinitrobenzene (FDNB)—70-34-8
2-Fluorobenzoyl chloride—393-52-2
Formaldehyde—50-00-0
Furfural—98-01-1
Gallic acid—149-91-7
Gluteraldehyde—111-30-8
Hemotoxylin
Hexabromobenzene—87-82-1
Hexabromobiphenyl—36355-01-8
Hexachlorobenzene—118-74-1
Hexachlorocyclopentadiene dimer—2385-85-5
Hexachloroethane—67-72-1
Hexachlorophene—70-30-4
Hexaclorobutadien—87-68-3
Hexamethly-p-rosaniline-ci—548-62-9
Hydrazine sulfate—10034-93-2
Hydrazinobenzene—100-63-0
Hydroquinone—123-31-9
Hydroquinone dimethyl ether—150-78-7
Hydroquinone monomethyl ether—150-76-5
4-Hydroxyacetanilide—103-90-2
Ligninsulfonic acid sodium salt—8062-15-5
Lithium chloride—7447-41-8
Maleic anhydride—108-31-6
Maleic hydrazide—123-33-1
Melamine—108-78-1
Metchloronitrobenzene—121-73-3
Methacrylic acid methylester—80-62-6
Methylhydrazine—60-34-4
N-Methyl-para-aminophenol—150-75-4
3-Methyl-3-phenylglycidic acid ethyl ester—77-33-8
Methyl salicylate—119-36-8
Ortho-methoxyphenol—90-05-1
8-Methoxyphenol—298-81-7
8-Methoxy psoralin
Morpholine—110-91-8
Neophytadiene—504-96-1
Nickelocene—1271-28-9
1-Nitronaphthalene—86-57-7
p-Nitrophenol—100-02-7
2-Nitropropane—79-46-9
N-Nitrosodiethanolamine—1116-54-7
2-Nitro-α,α,α-trifluorotoluene
3-nitro-α,α,α-trifluorotoluene
Oxalic acid—144-62-7
Paraquat—4685-14-7
Pentachloroaniline—527-20-8
Pentachloroanisole—1825-21-4
Pentachlorobenzene—608-93-5
Pentachloronaphthalene—1321-64-8
Pentachloronitrobenzene—82-68-8
Pentachlorophenol—87-86-5
Pentachlorophenyl methyl ether—1825-21-4
Pentachlorophenyl methyl sulfide—1825-19-0
Phenyl salicylate—118-55-8
Phenytoin—57-41-0
Phorbol ester—17673-25-5
1-(2H)-Phthalazinone—119-39-1
Phthalic anhydride—85-44-9
Picric acid—88-89-1
Piperazine—110-85-0
Piperonal—120-57-0
Polybrominated biphenyl—
Propylene Dichloride—78-87-5
1,2-Propylene glycol—57-55-6
Pyridine—110-86-1
Quinoline—91-22-5
p-Quinone—106-51-4
Resorcinol—108-46-3
Rhodanine (Ammonium salt)—1762-95-4
Ricinoleic acid—141-22-0
Semicarbazide hydrochloride—563-41-7
Sodium aluminosilicate—1344-00-9
Sodium dehydroacetate-4418-26-2
Sodium dichloroisocyanurate—13023-28-4, 2893-78-9
Sodium fluoride—7681-49-4
cis-Stilbene—645-49-8
trans-Stilbene—645-49-8
Terephthalic acid—100-21-0
Tert-butyl hydroperoxide—110-05-4
1,2,3,5-Tetrachlorobenzene—634-90-2
1,2,3,4-Tetrachlorobenzene—634-66-2
1,2,4,5-Tetrachlorobenzene—95-94-3
Tetrachloroethylene—127-18-4
Tetrachloronitrobenzene—28804-67-3
Tetrachloronaphthalene
Tetrachlorophthalic anhydride—117-08-8
Tetrakis(hydroxymethyl)phosphonium chloride—124-64-1
Tetraethyllead—78-00-2
Tetramethyllead—75-74-1
Tetranitromethane—509-14-8
Thiazole—288-47-1
Thiocarbonilide
Thioglycolic acid—68-11-1
Toluene—108-88-3
Tributoxyethyl phosphate—Tributyl borate—688-74-4
1,2,3-Trichlorobenezene—87-61-6
1,2,4-Trichlorobenezene—120-82-1
1,3,5-Trichlorobenezene—108-70-3
Trichloronaphthalene—1321-65-9
2,4,6-Trichlorophenol—88-06-2
Triethanolamine—102-71-6
Triphenylphosphine—603-35-0
Trihydroxybutyrophenone—52262-23-4
Tris(4-bromophenyl)phosphate
Tris(2-chloroethyl)phosphite
Tris(2-ethylhexyl)phosphate—78-42-2
Tris(isopropylphenyl)phosphate
Tritolyl phosphate—1330-78-5
Wollastonite ca silicates
meta-Xylene—108-38-3
ortho-Xylene—95-47-6
para-Xylene—106-42-3

Table 5.—*Chemicals Selected for a Battery of Mutagenicity Assays*

Chemicals	CAS No.
Allyl chloride	107-05-1
Bisphenol A	80-05-7
Butylene oxide	26249-20-7
Cyclohexanone	108-94-1
N,N-dimethyl acetimide	
Dimethylformamide	68-12-2
Ethoxyethanol	110-80-5
Ethyl benzene	100-41-4
Ethylene oxide	75-21-8
Hexachlorobutadiene	87-68-3
Mercaptobenzenethiazole	149-30-4
Methyl bromide	74-83-9
2 Methoxyethanol	109-86-4
Bis 2 methoxyethoxyethyl ether	143-24-8
N methyl dicyclohexylamine	
Styrene oxide	100-42-5
1,1,2,2-tetrachlorethane	127-18-4
Vinyl toluene	

TABLE 6.—*International Collaborative Study of Mutagenicity Assay Systems; Compounds To Be Tested*

Carcinogen/Noncarcinogen Pairs	
4-Nitroquinoline-N-oxide—56-57-5	Chloroform—67-66-3
3-Methyl-4-nitroquinoline-N-oxide—14073-00-8	1,1,1-Trichloroethane—71-55-6
Benzidine—92-87-5	2-Acetylaminofluorene
3,3',5,5'-Tetramethylbenzidine—54827-17-7	4-Acetylaminofluorene
4-Dimethylaminoazobenzene (Butter Yellow)—60-11-7	N-Nitrosomorpholine—59-89-2
4-Dimethylaminoazobenzene-4-sulphonic acid	Diphenylnitrosamine—86-30-6
Sodium salt (Methyl Orange)	Dinitrosopentamethylene tetramine
Urethane—51-79-6	1-Naphthylamine—134-32-7
O-Isopropyl-N-3-chlorophenylcarbamate—101-21-3	2-Naphthylamine—91-59-8
Benzo(a)pyrene—	Dimethyl carbamoyl chloride—79-44-7
Pyrene—129-00-0	Dimethylformamide—68-12-2
Propiolactone—57-57-8	Methylazoxymethanol acetate—592-62-1
Butyrolactone—96-48-0	Azoxybenzene—495-48-7
9,10-Dimethylanthracene—781-43-1	d,1.Ethionine—
Anthracene—120-12-7	Methionine—63-68-3

Miscellaneous Compounds

Hydrazine sulphate—10034-93-2
Hexamethylphosphoramide (HMPA—680-31-9
Ethylenethiourea—96-45-7
Diethylstilbestrol—56-53-1
Safrole—94-59-7
Cyclophosphamide—50-18-0
Epichlorhydrin—
3-aminotriazole
4,4'-Methylenebis (2-chloroaniline)—101-14-4
Sugar (sucrose)—57-50-1
O-toluidine—95-53-4
Ascorbic acid—50-81-7
Auramine

Table 7.—*International Collaborative Study of Mutagencity Assay Systems Utilized*

Prokaryotic Systems

Repair deficiency assays:
- Bacillus subtilis—rec
- Escherichia coli—rec
- Escherichia coli—pol A

Point mutation assays:
- Salmonella typhimurium/microsome (Ames test)
- Salmonella typhimurium 8-azaquanine resistance
- Escherichia coli WP-2
- Escherichia coli 343-113

Eukaryotic Systems

Fungus:
- Saccharomyces cerevisiae—mitotic recombination
- Saccharomyces cerevisiae—reversions
- Schizosaccharomyces pombe—forward mutations
- Saccharomyces cerevisiae—mitochondrial mutations
- Neurospora crassa—ad-3 reversions

Plant:
- Tradescantia—stamen hair system

Insect:
- Drosophila melanogaster—sex-linked recessive lethals

Mammal (in vitro):
- Unscheduled DNA Synthesis (human cells)
- Sister chromatid exchange (CHO cells)
- Chromosome aberrations (hamster and rat cells)
- Specific Locus mutations—
  - L5178Y cells—TK and HGPRT
  - P388F cells—TK and HGPRT
  - CHO cells—HGPRT
  - Human fibroblasts—HGPRT

Mammal (in vivo):
- Micronucleus (mouse)
- Chromosome aberrations
- Sister-chromatid exchange (mouse, rabbit)
- Sperm morphology (mouse)

Nongenetic Systems

- Hydroxylation of Biphenyl
- Local Graying of Hair
- *In vitro* Nuclear Enlargement
- Rabins Test
- Transformation (BHK Cells)

Table 8.—*Chemicals for Which Lifetime Bioassays Are In Progress*

Chemical	CAS No.	Route	Spec.
Acid black 52		Feed, intratr	RH
Acid orange #3	6373-74-6	Feed	RM
Agar agar	9002-18-0	Feed	RM
Agaritine	2757-90-6	Water	RM
Aldicarb	116-06-3	Feed	RM
Allyl isothiocyanate	57-06-7	Gav	RM
Allyl isovalerate	2835-39-4	Gav	RM
Aminoundecanoic acid	27323-47-3	Feed	RM
Aniline, p-chloro-	106-47-8	Feed	RM
Antimony oxide	1309-64-4	Feed	RM
Asbestos, amosite		Feed	RH
Asbestos, chrysotile SR		Feed	RH
Asbestos, chrysotile IR		Feed	RH
Asbestos, chrysotile SR		Inhal	R
Asbestos, chrysotile IR		Inhal	R
Asbestos, crocidolite		Feed	R
Ascorbic acid	50-81-7	Feed	RM
Benzene	71-43-2	Gav	RM
Benzoin	119-53-9	Feed	RM
Benzyl acetate	140-11-4	Gav	RM
Benzyl chloride	100-44-7	IP/IJ	M
2-biphenylamine HCl	90-41-5	Feed	RM
Bisphenol A	80-05-7	Feed	RM
HC blue 1	2784-94-3	Feed	RM
Blue 15B	574-93-6	Feed	RM
Bromoform	75-25-2	Gav	RM
Bromodichloromethane	75-27-4	Gav	RM
Butylated hydroxytoluene (BHT)	128-37-0	Feed	RM
Butyl benzyl phthalate	85-68-7	Feed	RM
n-Butyl chloride	106-69-3	Gav	RM
t-Butyl alcohol	75-65-0	Water	RM
Caprolactam	105-60-2	Feed	RM
Castor oil	8001-79-4	Feed	RM
Chlorobenzene	108-90-7	Gav	RM
Chlorodibromomethane	124-48-1	Gav	RM
3-Chloro-2-methylpropene	563-47-3	Gav	RM
C.I. disperse yellow 3	2832-40-8	Feed	RM
Cinnamyl anthranilate	87-29-6	Feed	RM
Coconut oil acid diethanolamine (con 2/1)	8040-31-1	SP	RM
Cyclohexanone	108-94-1	Water	RM
Cytembena	2126-70-7	IP/IJ	RM
D & C red No. 9	5160-02-1	Feed	RM
DBCP	96-12-8	Inhal	RM
Decabromodiphenyl oxide	1163-19-5	Feed	RM
Diallylphthalate	131-17-9	Gav	RM
Dibenzo-p-dioxin, 1,2,3,6,7,8-hexachloro	34465-46-8	SP	M
Dibenzo-p-dioxin, 1,2,3,6,7,8-hexachloro	34465-46-8	Gav	RM
Dibenzo-p-dioxin, 2,3,7,8-tetrachloro	1746-01-6	SP	M
Dibenzo-p-dioxin, 2,3,7,8-tetrachloro	1746-01-6	Gav	RM
Diesel fuel marine		Gav	R
Diesel fuel marine		SP	M
1,4-diamino-2,6-dichlorobenzene		Feed	RM
o-Dichlorobenzene	95-50-1	Gav	RM
p-Dichlorobenzene	106-46-7	Gav	RM
1,1-dichloroethylene	75-35-4	Gav	RM
Cis/trans-1,2-dichloroethylene	156-59-2 540-59-0	Gav	RM
1,2-dichloropropane	78-87-5	Gav	RM
Diethanolamine	111-42-2	Water	RM
Di(2-ethylhexyl)adipate	103-23-1	Feed	RM
Di(2-ethylhexyl)phthalate	117-81-7	Feed	RM
Diglycidylresorcinol ether	101-90-6	Feed	RM
n,n-Dimethyldodecylamine oxide	1643-20-5	Water	RM
Dimethylhydrogenphosphite	868-85-9	Gav	RM
Dimethyl methylphosphonate	756-79-6	Gav	RM
Dimethyl morpholinophosphonate	597-25-1	Gav	RM
Dimethylvinylchloride	513-37-1	Gav	RM
Diphenylamine, n-nitroso	86-30-6	Feed	RM
4,4'-diphenylmethane diisocyanate	101-68-8	Gav	RM
Disperse blue #1	2475-45-8	Feed	RM
Disperse yellow #3		Feed, intratr	RH
Dodecyl alcohol, ethoxylated	29718-44-3	Feed	RM
Ethane, 1,2-dibromo	106-93-4	Inhal	RM
Ethane, 1,1,1-trichloro	71-55-6	Gav	RM
Ether, bis(2-chloro-l-methylethyl)	108-60-1	Gav	M
Ether, bis(2-chloro-l-methylethyl)	108-60-1	Gav	R
Ethyl acrylate	140-88-5	Gav	RM

Table 8.—*Chemicals for Which Lifetime Bioassays Are In Progress—Continued*

Chemical	CAS No.	Route	Spec.
Ethyl tellurac	30145-38-1	Feed	RM
Ethylene chlorohydrin	107-07-3	SP	RM
Ethylene glycol monoethyl ether	110-80-5	Water	RM
Eugenol	97-53-0	Feed	RM
Fibrous glass		Inhal	R
Fluometuron	2164-17-2	Feed	RM
Fluorescein, disodium salt	518-47-8	Water	RM
Geranyl acetate	105-87-3	Gav	RM
Gilsonite	12002-43-6	SP	RM
Guar gum	9000-30-0	Feed	RM
Gum arabic	9000-01-5	Feed	RM
Gum tara		Feed	R
HC blue #2		Feed	RM
HC red #3		Feed	RM
8-hydroxyquinoline	148-24-3	Feed	RM
Lauric acid diethanolamine (Con I/I)	120-40-1	SP	RM
Lead dimethyl dithiocarbamate	19010-66-3	Feed	RM
Locust beam gum	9000-40-2	Feed	RM
Malaoxon	1634-78-2	Feed	RM
Malathion	121-75-5	Feed	R
Maleic hydrazide diethanolamine salt	5716-15-4	Water	RM
Malonaldehyde	542-78-9	Gav	RM
Mannitol	69-65-8	Feed	RM
Melamine	108-78-1	Feed	RM
Methapyrilene	91-80-5	Feed	RM
Methylenedianiline	101-77-9	Feed	RM
Methylene chloride	75-09-2	Gav	RM
Methylene chloride	75-09-2	Inhal	RM
Mirex	2385-85-5	Feed	R
Molybdate orange	12656-85-8	Feed	RM
Monuron	150-68-5	Feed	RM
Naphthalene	91-20-3	Gav	RM
Nitrofurantoin	67-20-9	Feed	RM
Oleic acid diethanolamine (Con I/I)	13961-86-9	SP	RM
Orange #10	1936-15-8	Feed	RM
4,4'-oxydianiline	101-80-4	Feed	RM
Pentachloroethan	76-01-7	Gav	RM
Phenol	108-95-2	Water	RM
Phenylbutazone	50-33-9	Water	RM
Phenytoin		Feed (prenatal/ postnatal).	RM
Phthalocyanine green	1328-53-6	Feed	RM
Polychlorinated biphenyl		Feed (prenatal/ postnatal).	RM
Propyl gallate	121-79-9	Feed	RM
Pyridine	110-86-1	Gav	RM
Red #14	3567-69-9	Feed	RM
Reserpine	50-55-5	Feed	RM
p-Rosaniline HCl	569-61-9	Feed	RM
Selenium sulfide	7488-56-4	Gav	RM
Selenium sulfide	7488-56-4	SP	M
Selsun	UNK	SP	M
Sodium dodecyl sulfate	151-21-3	Feed	RM
Sodium(2-ethylhexyl)alcohol sulfate	126-92-1	Feed	RM
Stannous chloride	7772-99-8	Feed	RM
Styrene oxide	96-09-3	Gav	RM
Sudan 1	842-07-9	Feed	RM
Sun yellow FCF	2783-94-0	Feed	RM
Telone	542-75-6	Gav	RM
1,1,1,2-tetrachloroethane	630-20-6	Gav	RM
Tetrachloroethylene	127-18-4	Inhal	RMH
Tetraethylthiuram disulfide	14239-68-0	Feed	RM
THPC	124-64-1	Feed	RM
THPS	UNK	Feed	RM
Toluene diisocyanate	584-84-9	Gav	RM
Tremolite		Feed	R
Trichlorfon	52-86-6	Feed	RM
Trichloroethylene	79-01-6	Gav	RM
Tris(2-ethylhexyl)phosphate	78-42-2	Gav	RM
Violet 3	1325-82-2	Feed	RM
Witch hazel	84400-12-7	SP	RM
Zearalenone	7645-23-0	Feed	RM
Ziram	137-30-4	Feed	RM

Table 9.—*Chemicals selected for Extensive Evaluation of Toxic Effects Including Carcinogenesis*

Compound	NCI No.	CAS No.
2-Amino-4-nitrophenol	C55958	99-57-0
2-Amino-5-nitrophenol	C55970	121-88-0
Ampicillin	C56086	69-53-4
Amyl nitrite (butyl nitrite)	C50179	110-46-3
Arsenicals, organic		
Benzathine penicillin G	C56100	1538-0-6
Benzofuran	C56166	271-89-6
Benzyl alcohol	C06111	100-51-6
2,2-Bis(bromomethyl)-1,3-propanediol.	C55516	3296-90-0
Boric acid		11113-50-1
Bromobenzene	C55492	108-86-1
1,3-Butadiene	C50602	106-99-0
2-Butanone peroxide	C55447	1338-23-4
Caffeine	C02733	58-08-2
Capsaicin		404-86-4
Carbon disulfide	C04591	75-15-0
Chloramine	C56382	55-86-7
Chlorendic acid	C55072	115-28-6

Table 9.—*Chemicals selected for Extensive Evaluation of Toxic Effects Including Carcinogenesis*—Continued

Compound	NCI No.	CAS No.
Chlorinated trisodium phosphate.	C55754	56802-99-4
Chloroacetophenone	C55107	532-27-4
Chlorobenzalmalononitrile	C55118	
Chlorowax 40	C53543	61990-12-6
Chlorowax 500	C53567	56509-64-9
Chlorpheniramine maleate		113-92-8
Cineol (eucalyptol)		470-67-7
Cinnamaldehyde	C56111	104-55-2
2,3-Dibromo-I-propanol	C55436	96-13-9
1,4-Dichlorobenzene	C54955	106-46-7
2,4-Dichlorophenol	C55345	120-83-2
Dichlorvos	C00113	62-73-7
Dimethylaniline	C56188	87-62-7
Diphenhydramine HCL	C56075	147-24-0
DMBA (positive control)	C03918	57-97-6
Ephedrine sulphate	C55652	299-42-3
Epinephrine HCL	C55663	55-31-2
1,2-Epoxybutane	C55527	106-88-7
1,2-Epoxyhexadecane	C55538	7320-37-8
Erythromycin stearate	C55674	114-07-8
Ethyl alcohol	C03134	64-17-5
Ethylbenzene		100-41-4
Ethyl bromide	C55481	74-96-4
Ethyl chloride	C06224	75-00-3
Ethylene oxide	C50088	75-21-8
Formaldehyde	C02799	50-00-0
Furosemide	C55936	54-31-9
Gibberellic acid	C55823	77-06-5
Glutaraldehyde	C55425	111-30-8
Glycidol	C55549	556-52-5
Hematoxylin	C55889	517-28-2
Hexabromobiphenyl (FF-1)	C53634	36355-01-8
Hexafluoroacetone	C08413	10057-27-9
Hexamethyl-p-rosaniline (gentian violet).	C55969	548-62-9
Hexylresorcinol	C55787	136-77-6
Hydrochlorothiazide	C55925	58-93-5
Hydroquinone	C55834	123-31-9
5-Hydroxytryptophan		56-69-9
Iodinated glycerol	C55469	5634-39-9
Isophorone	C55618	78-59-1
Isopropyl glycidyl ether		
d-Limonene	C55572	5989-27-5
Mercaptobenzothiazole		149-30-4
8-Methoxypsoralen	C55903	298-81-7
Methylbenzyl alcohol	C55685	98-85-1
Methyl carbamate	C55594	598-55-0
Methyldopa	C55721	555-30-6
Methyl methacrylate	C50680	80-62-6
Mycotoxins (ochratoxin, penicillic acid).		
Nalidixic acid	C56199	389-08-2
Naphthalene		91-20-3
2-Napthylamine, N pehnyl	C02915	135-88-6
5-Nitro-2-furaldehyde		698-63-5
Nitrofurazone	C56064	59-87-0
Oil of nutmeg		
Oxalic acid	C55209	144-62-7
Pentachloroanisole		1825-21-4
Pentachloronitrobenzene	C00419	82-68-8
Pentachlorophenol	C54933	87-86-5
Phenol	C50124	108-95-2
Phenolphthalein	C55798	77-09-8 5768-87-6
Phenylephrine hydrochloride	C55641	61-76-7
o-Phenylphenol	C50351	90-43-7
Polyurethane		9009-54-5
Propylene	C50077	115-07-1
Propylene oxide	C50099	75-56-9
Pyrrolizidine alkaloids		643-20-9
Retene	C55390	483-65-8
Rhodamine 6G	C56122	989-38-8
Rotenone	C55210	83-79-4
Sodium aluminosilicate	C55505	1344-00-9
Sodium dichloroisocyanurate	C55732	2893-78-9
Sodium fluoride	C55221	7681-49-4
Succinic anhydride	C55696	108-30-5
Sucrose		25702-74-3 9012-95-7 27616-49-5
Sulfamethazine		57-68-1
2,3,7,8-Tetrachlorodibenzofuran.		51207-31-9
Tetrachloroethylene (perchloroethylene).	C04580	127-18-4
Tetracycline hydrochloride	C55561	64-75-5
Tetracycline, oxy	C05209	79-57-2
Tetranitromethane	C55947	509-14-8
Tocopherol		1406-66-2
Toluene	C07272	108-88-3
Trimellitic anhydride		552-30-7
Vinylcyclohexene	C54999	106-84-1
Vinyl toluene		622-97-9
Wollastonite Ca-silicates	C55470	13983-17-0
Xylenes, mixed	C55992	1330-20-7

TABLE 10.—*Chemicals nominated for Toxicologic or Carcinogenic Evaluation*

Compound	NCI No.	CAS No.
1-amino-2, 4-dibromoanthraquinone.		81-49-2
amphetamine	C55710	60-13-9
azodicarbonamide	C55981	123-77-3
benzaldehyde	C56133	100-52-7
benzilic acid, 4,4'-dichloroethyl ester.	C00408	510-15-6
N-butyl chloride	C06155	109-69-3
gama-butyrolactone	C55878	96-48-0
beta-cadinene (oil of cade)	C56008	523-47-7
carvone (caraway, dill seed)	C55867	99-49-0
catechol	C55856	120-80-9
chloramphenicol	C55709	56-75-7
chlordecone (Kepone)	C00191	143-50-0
chlorinated dibenzofurans		
chlorinated naphthalenes		
p-chloroaniline	C02039	106-47-8
chlorpromazine	C05210	69-09-0
chromium inorganic	C04273	7440-47-3
copper and inorganic compounds.	C08515	7440-50-8
corn oil	C00577	8001-30-7
curcumin		458-37-7
2,4-diaminophenol hydrochloride.		
4,4-diamino-2,2'-stilbenedisulfonic acid.		
cis-dichlorodiamine platinum (II).	C55776	15663-27-1
1,1-dichloroethylene	C54262	75-35-4
cis- & trans-1,2-dichloroethylene.	C51581	156-59-2
dichloropropane		26638-19-7
diethyl phthalate		84-66-2
3,4-dihydrocoumarin	C55890	119-84-6
dimethoxane ("dioxin")	C56213	828-00-2
3-3'dimethoxybenzidine	C02175	91-93-0
dimethyl sulfoxide	C00873	67-68-5
ethoxyethanol	C54853	110-80-5
ethylene glycol	C00920	107-21-1
furan	C56202	110-00-9
furfural	C56177	98-01-1
furfuryl alcohol	C56224	98-00-0
glycol	C00817	9005-65-6
H C yellow No. 4	C56019	52551-67-4
hexachlorobutadiene		87-68-3
hexachlorocyclopentadiene	C55607	77-47-4
hexachloroethane	C04604	67-72-1
hormones		
hydroxyacetanilide		
4-hydroxyacetanilide	C55801	103-90-2
indomethacine	C56144	53-86-1
iron compounds		
isoproterenol HCL	C55630	7683-59-2
lead oxide		1335-25-7
lithium and compounds		7439-93-2
manganese compounds	C02517	7439-96-5
mercury (metal)	C04375	7439-97-6
mercuric chloride		7487-94-7 43412-44-8
phenyl mercuric acetate		
methapyriline	C09018	91-80-5
methyl coumarin	C55812	92-48-8
o-methylhydroxylamine		67-62-9
methyl ethyl ketone peroxide		1338-23-4
monochloroacetic acid	C08264	79-11-8
monochloroethane		75-003
monosodium methane arsenate.		
navy fuels JP-5	C54784	
nitrobenzene		98-95-3
nitrophenols		
p-nitropenol	C55992	100-02-7
N-nitrosodiethanolamine	C55583	1116-54-7
nitrotoluene		1321-12-6
octachlorodibenzodioxin	C03678	3268-87-9
oleic acid, methyl ester, cis		
organophosphates		
palladium (2+) chloride		
pentachloroethane	C53894	76-01-7
pentaerithritol tetranitrate	C55743	78-11-5
petroleum distillates		
phenol, 2,2'-thiobis(4,6-dichloro).	C02948	97-18-7
D-phenylalanine		673-06-3
N-phenylhydroxylamine		100-65-2
pichloram	C00937	1918-02-1
platinum and compounds		7440-06-4
polyvinylpyrrolidone polymers		
potassium azide		20762-60-1
probenecid	C56097	57-66-9
quercetin		522-12-3
p-quinone	C55845	106-51-4
resorcinol	C05970	108-46-3
rhodamine	C56122	989-38-8
sodium azide	C06462	26628-22-8
sodium dichloroisocyanurate	C55732	2893-78-9
styrene	C02200	100-42-5
talc	C06009	14807-96-6
L-taurine		107-35-7
tellurium		13494-80-9
tetrahydrofuran		109-99-9
tetrakis (hydroxymethyl) phosphonium chloride.	C55061	124-64-1
titanium & compounds—titanium.	C04251	7440-32-6
titanium oxide	C04240	13463-67-7
titanium ferrocene	C04502	1271-19-8
trichloroethylene	C04546	79-01-6
trichloropropane		25735-29-9
2,4,6-trinitrotoluene	C56155	118-96-7
tris (4-bromophenyl) phosphate.		
tris (2-chloroethyl) phosphate		115-96-8
vinyl cyclohexene dioxide		
vinylidene fluoride		
vitamin D		1406-16-2
vitamin D_3		67-97-0
witch hazel	C50544	84400-12-7
xylenesulfonic acid, sodium salt.	C55403	1300-72-7
2,6-xylidine	C56188	87-62-7

Table 11.—*Chemicals Studied for Behavioral or Neurologic Effect*

Chemicals	CAS No.
Carbon disulfide [a]	75-60-5
Chlordecone	143-50-0
Caffeine [b]	58-08-2
Ethanol [b]	64-17-5
Ethylene oxide	75-21-8
Lithium carbonate	554-13-2
Mercaptobenzothiazole	149-30-4
Methyl bromide	74-83-9
Methyl chloride [b]	74-87-3
Methylethyl ketone [c]	78-93-3
Polybrominated biphenyl	
Propylene oxide	75-56-9
Selenium	7488-56-4
Toluene [c]	108-88-3
Valium [b]	439-14-5
Xylene	1330-20-7

[a] Human subject study.

[b] Includes human subject study and interaction of methyl chloride, caffeine, ethanol and valium.

[c] Includes human subject study and interaction of toluene, methyl ethyl ketone, and xylene.

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